COMMENTARY

# Using Apolipoprotein B to Manage Dyslipidemic Patients: Time for a Change?

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Low-density lipoprotein cholesterol (LDL-C) concentration has been established as an independent risk factor for the development of atherosclerosis; consequently, multiple practice guidelines recognize LDL-C as the primary target of therapy.[1,2] For decades, considerable effort has been committed to educating physicians and the general public about the importance of lowering LDL-C levels.

Despite the extensive data relating LDL-C to atherosclerosis, some have suggested that focusing only on LDL-C may not be an optimal strategy.[3] Several limitations exist for an approach that focuses only on LDL-C: (1) evidence is increasing that triglyceride-rich lipoproteins, including very low-density lipoproteins (VLDL) and intermediate-density lipoproteins (IDL) (Figure 1)[4] are also atherogenic[5,6]; and (2) a substantial percentage of patients with atherosclerotic vascular disease have LDL-C in the optimal range.[7] Furthermore, many patients who receive treatment and achieve recommended LDL-C goals even lower than 70 mg/dL (to convert to mmol/L, multiply by 0.0259) still develop the complications of atherosclerotic vascular disease, which is referred to as *residual risk*.[8] One explanation for these discrepancies is the mismatch that has been described in many patients between the LDL-C concentration reported on a basic lipid panel and the number of atherogenic lipid particles, which is often expressed as low-density lipoprotein (LDL) particle number or the number of apolipoprotein B (apo B)–containing lipoproteins.[9] The reason for this mismatch is that LDL particles are extremely heterogeneous with respect to the amount of cholesterol contained in the LDL particle core.[10] Patients with a predominance of cholesterol-depleted LDL particles (also called small dense LDL-C) may have a low LDL "cholesterol" concentration as reported on the standard lipid panel but still have a large number of circulating atherogenic LDL particles.[11] For example, 2 patients with the same LDL-C concentration on a basic lipid panel may have markedly different LDL particle numbers and different cardiovascular risk (Figure 2).[12] Extrapolating information concerning the number of atherogenic LDL particles from the LDL-C content is an unreliable strategy.

Recently, some expert panels and national organizations have proposed using apo B in conjunction with standard lipid testing to address the aforementioned limitations.[13] Apo B is a key structural component of all the atherogenic lipoprotein particles, including LDL, VLDL, and IDL. Each of these atherogenic particles carries only one apo B molecule; thus, the total apo B level represents the total number of circulating atherogenic lipoprotein particles and provides the clinician a more accurate picture of a patient's risk of cardiovascular events.[13] Other advantages to the measurement of apo B include the fact that it does not require a fasting specimen, its relative low cost, and the existence of a World Health Organization–approved standard.

Alternatively, some experts advocate calculating and using non–high-density lipoprotein cholesterol (non–HDL-C) instead of LDL-C to improve risk prediction in certain groups of patients, particularly in those with elevated triglyceride values.[1] The National Cholesterol Education Program (NCEP)/Adult Treatment Panel (ATP) III guidelines recommend that, in patients with triglyceride levels of 200 mg/dL or higher, non–HDL-C should be calculated and the goal set at 30 mg/dL higher than the LDL-C goal (Table1).[1] Substantial evidence supports the idea that non–HDL-C is clearly superior to LDL-C for cardiovascular disease risk prediction. Non–HDL-C is calculated by subtracting the HDL-C from the total cholesterol, and it represents the cholesterol concentration of all atherogenic lipoproteins.[14,15] Although non–HDL-C is a good surrogate measure of apo B, it does not measure the same thing. Non–HDL-C measures the "cholesterol" content of all atherogenic lipoproteins (LDL, IDL, and VLDL), whereas apo B represents the total number of circulating atherogenic particles. Although substantial evidence supports the idea that non–HDL-C is clearly superior to LDL-C for cardiovascular disease risk prediction, strong evidence shows that apo B may be superior to both LDL-C and non–HDL-C for both risk stratification and determination of goal attainment during therapy.

In this commentary, we propose how apo B might be used by clinicians involved in the primary and secondary prevention of coronary heart disease. First, we briefly discuss the evidence that suggests the superiority of apo B as a

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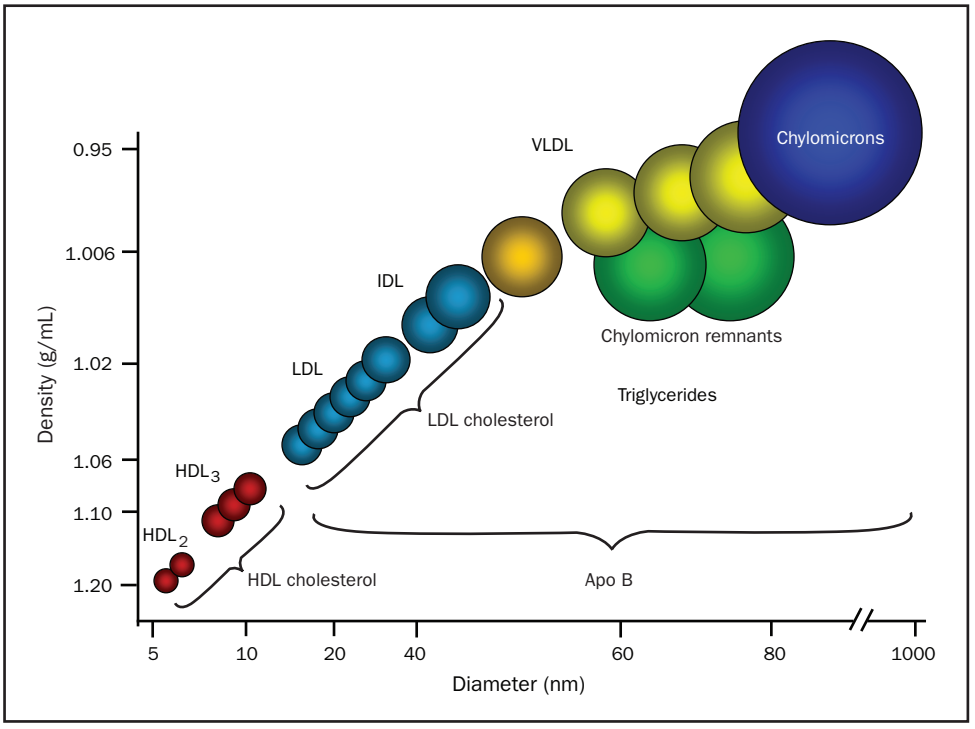


FIGURE 1. Lipoprotein subclasses and apolipoprotein (apo) B–containing lipoproteins. HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein.
Adapted from *J Clin Lipid*,[4] with permission.

risk predictor compared to non–HDL-C and LDL-C. Then, we suggest certain patient populations in whom clinicians may wish to target apo B because of demonstrated superiority to LDL-C, including those with diabetes and those receiving statin therapy. Finally, we discuss current recommendations for apo B goals of therapy and the evidence for these goals.

## Evidence Demonstrating the Superiority of Apo B to Non–HDL-C and LDL-C for Cardiovascular Risk Prediction

Multiple epidemiological and clinical trials support the superiority of apo B for risk prediction compared to both LDL-C and non–HDL-C (Table 2).[16-25] Recently, the large epidemiological study AMORIS (*A*polipoprotein related *Mo*rtality *Ris*k) recruited more than 175,000 Swedish men and women and monitored them for more than 5 years.[16] Total cholesterol, apo B, and apo A1 levels were measured, and LDL-C values calculated. The association between death from acute myocardial infarction and initial values for apo B, apo A1, and LDL-C was analyzed. In multivariate analysis, apo B was a stronger predictor of risk than LDL-C. Apo B also demonstrated a higher sensitivity and specificity than LDL-C as a predictive variable in both men and women irrespective of whether the data were adjusted for age.

Another example is the INTERHEART study. INTERHEART is a large standardized case-control study of acute myocardial infarction in more than 12,000 cases and more than 14,000 age-matched and sex-matched controls from 52 countries and several ethnic groups. Apo B had the highest odds ratio of any single measure for the prediction of risk of coronary heart disease and was superior to non–HDL in all ethnic groups.[17]

## Usefulness of Apo B Measurements in Diabetic Patients and Patients at High Cardiometabolic Risk

Diabetic patients and patients with multiple cardiometabolic risk factors (obesity, insulin resistance, and hypertension) are populations in whom apo B measurement may be most advantageous. Focusing on the basic lipid panel and LDL-C alone may result in an underestimation of cardiovascular risk. Diabetic dyslipidemia is frequently characterized by multiple lipoprotein abnormalities, including elevated levels of triglyceride-rich lipoproteins such as VLDL and IDL, increased numbers of small dense LDL particles, and low levels of HDL-C.[13] Because there is one apo B molecule per

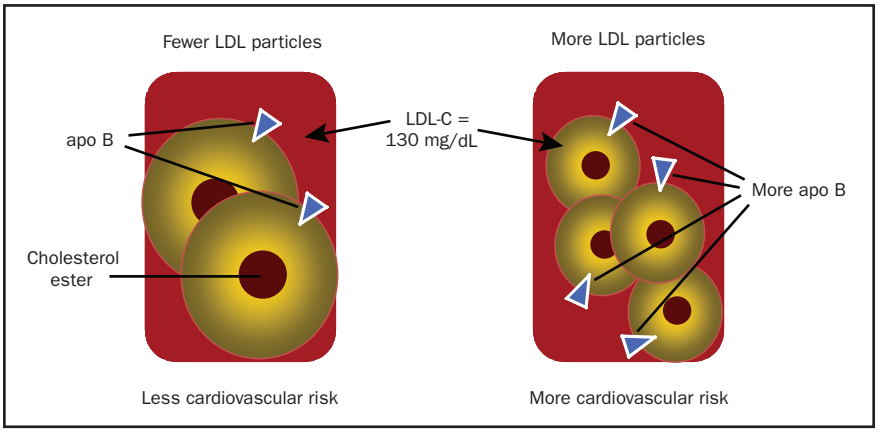


FIGURE 2. Same low-density lipoprotein cholesterol (LDL-C) levels, different cardiovascular risk. apo = apolipoprotein. SI conversion factors: To convert LDL-C value to mmol/L, multiply by 0.0259. Adapted from *Am J Cardiol,*[12] with permission.

particle of VLDL and IDL, apo B measurement could be used as an effective marker for elevations in these atherogenic triglyceride-rich lipoproteins and a more accurate predictor of cardiovascular risk.

### Usefulness of Apo B for Assessment of Risk in Patients Receiving Lipid-Lowering Therapy

Support is increasing for measurement of apo B to improve the assessment of "residual risk" in patients being treated with lipid-lowering drugs. Patients receiving therapy still have significant residual cardiovascular risk even with treatment to reach aggressive LDL-C goals. Factors that contribute to residual risk include elevated levels of atherogenic lipoprotein particles other than LDL, such as IDL and VLDL, and the presence of small dense LDL particles not detected in a basic lipid panel. Measurement of apo B detects the presence of all atherogenic particles and has led some experts to recommend monitoring apo B along with LDL-C to better determine residual risk and therapeutic effectiveness. This recommendation has led some experts to suggest monitoring of apo B to better determine "residual" cardiovascular risk in patients receiving therapy and to target both LDL-C and apo B for monitoring therapeutic effectiveness.[13]

In fact, several clinical trials have demonstrated the superiority of apo B to LDL-C in monitoring patients receiving statin therapy for residual risk. One such trial is AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study).[22] This post hoc analysis of the 6600 participants receiving lovastatin for 1 year was performed to identify lipid variables related to an acute major coronary event. At baseline, the association between LDL-C and apo B levels and the risk of a major coronary event was similar. However, after 1 year of treatment, the association between LDL-C and the risk of a major coronary event was not significant (*P*=.162). In contrast, after 1 year of treatment, apo B was a strong predictor of major coronary events (*P*=.001).

In another post hoc analysis, data were combined from 2 prospective secondary prevention trials: TNT (Treating to New Targets) and IDEAL (Incremental Decrease in End

TABLE 1. **ATP III LDL-C Goals and Cutpoints for Drug Therapy**[a]

| | Goal (mg/dL[b]) | |
|---|---|---|
| Risk category | LDL-C | Non–HDL-C |
| Very high risk[c] | <100 (optional <70) | <130 (optional <100) |
| High risk: CHD[d] or CHD risk equivalent[e] | <100 | <130 |
| Moderately high risk: ≥2 risk factors[f] (10-y risk, 10%-20%)[6] | <130 (optional <100) | 160 (optional <130) |
| Moderate risk: ≥2 risk factors[f] (10-y risk <10%) | 130 | 160 |
| Lower risk | 160 | 190 |

[a] ATP = Adult Treatment Panel; CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol; non–HDL-C = non–high-density lipoprotein cholesterol.

[b] SI conversion factors: To convert LDL-C and non–HDL-C values to mmol/L, multiply by 0.0259.

[c] Very high risk is defined as the presence of established cardiovascular disease plus diabetes, or plus multiple poorly controlled risk factors, or multiple risk factors of the metabolic syndrome (especially high triglycerides >200 mg/dL), or patients with acute coronary syndrome.

[d] CHD includes history of myocardial infarction, unstable angina, coronary artery procedures (bypass or angioplasty), or evidence of clinically important myocardial ischemia.

[e] CHD risk equivalents are defined as clinical manifestations of noncoronary atherosclerotic disease, including peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease (transient ischemic attacks or stroke of carotid origin or >50% obstruction of carotid artery), diabetes, and ≥2 risk factors with 10-y risk of hard CHD >20%.

[f] Risk factors include cigarette smoking, hypertension (blood pressure, >140/90 mm Hg or antihypertensive medication), low HDL-C (<40 mg/dL), family history of CHD in first-degree relative, or age (>45 y in men, >55 y in women).

From *JAMA,*[1] with permission.

TABLE 2. **Epidemiological Studies and Clinical Trials in Which Apo B Levels are Superior to LDL-C and Non–HDL-C Levels**

| Study name | Study type | No. of patients | Sex | Patient population |
|---|---|---|---|---|
| AMORIS[16] | Epi | 175,553 | M+F | Asymptomatic |
| INTERHEART[17] | Epi | 31,465 | M+F | Post-MI |
| NHANES[18] | Epi | 9500 | M+F | Asymptomatic |
| IDEAL[19] | CT | 8888 | M+F | Post-MI |
| LIPID[20] | CT | 4502 | M+F | CHD |
| Chinese Heart study[21] | Epi | 3586 | M+F | Asymptomatic |
| AFCAPS /TexCAPS[22] | Epi | 3301 | M+F | Asymptomatic |
| Casale Monferrato[23] | Epi | 1565 | M+F | Diabetes |
| Leiden Heart study[24] | CT | 848 | M | CHD |
| Health Professionals Follow-up study[25] | Epi | 532 | M | Asymptomatic |

AMORIS = *A*polipoprotein related *Mor*tality *Ris*k; AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; Apo B = apolipoprotein B; CHD = coronary heart disease; CT = clinical trial; Epi = epidemiological study; IDEAL = Incremental Decrease in End Points through Aggressive Lipid Lowering; NHANES = National Health and Nutrition Examination Survey; LIPID = Long-term Intervention with Pravastatin in Ischemic Disease; LDL-C = low-density lipoprotein cholesterol; non–HDL-C = non–high-density lipoprotein cholesterol; post-MI = post myocardial infarction.

Points through Aggressive Lipid Lowering). The strengths of associations of LDL-C, non–HDL-C, and apo B with the occurrence of major cardiovascular events while patients were receiving treatment were analyzed. The hazard ratios (HRs) were significant for LDL-C (HR, 1.15; 95% confidence interval [CI], 1.10-1.20), non–HDL-C (HR, 1.19; 95% CI, 1.14-1.25), and apo B level (HR, 1.19; CI, 1.14-1.24). In pair-wise comparisons, LDL-C was not significant as a predictor when combined with the apo B level or the non–HDL-C level, whereas apo B and non–HDL-C remained significant at HRs of 1.24 and 1.31, respectively. Thus, in statin-treated patients in TNT and IDEAL, levels of apo B and non–HDL-C were more closely associated with cardiovascular outcome than levels of LDL-C while patients were receving treatment.[26]

One of the reasons apo B may be superior to LDL-C in assessing the cardiovascular risk of patients receiving statin therapy is that statin therapy reduces LDL-C levels by a greater percentage than it does apo B levels; thus, it alters the association of LDL-C (LDL cholesterol content) to LDL particle number, resulting in many patients reaching their LDL-C goal but continuing to have a high number of LDL particles.

This concept of a mismatch between LDL-C and LDL particle number is illustrated in the MERCURY (Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapY) II trial, a 16-week trial consisting of more than 1900 patients at high risk of coronary heart disease or recurrent cardiac events.[27] Patients were randomized to treatment with rosuvastatin, atorvastatin, or simvastatin to compare the efficacy and safety of the most widely prescribed statins. In untreated patients, an LDL-C level of 100 mg/dL was approximately equivalent to an apo B level of 90 mg/dL. However, in patients receiving treatment with statins, the association between LDL-C and apo B was altered. In patients treated with a statin to an LDL-C goal of less than 100 mg/dL, only 48% reached their apo B goal of less than 90 mg/dL, thus underscoring that a significant number of patients have elevated apo B levels despite achievement of LDL-C goals. To consistently reach an apo B goal of less than 90 mg/dL required achievement of an LDL-C goal of less than 70 mg/dL (for patients with a high triglyceride level at baseline) or less than 80 mg/dL (for patients with a low triglyceride level at baseline). Results similar to MERCURY II were observed in an analysis by Sniderman[28] of 11 statin trials representing more than 17,000 patients. While patients were receiving treatment, the mean LDL-C concentration was 99.2 mg/dL, representing the 21st percentile of the population, whereas the mean apo B concentration was 101.6 mg/dL, representing the 55th percentile (Table 3).[28] Thus, a clear discordance between population percentiles for achieved LDL and apo B goals was again noted. This discordance illustrates how patients with optimal LDL-C levels may still be at high risk of cardiovascular events secondary to an undetected high number of LDL or apo B particles. Identifying patients with optimal or near optimal LDL-C levels yet high LDL particle number could result in more effective prevention of cardiovascular events.

## Goals of Therapy

The American Diabetes Association/American College of Cardiology (ADA/ACC) Consensus Conference Report (Table 4)[13] and the Canadian Cardiovascular Society[2] have suggested apo B goals for treatment of dyslipidemia and prevention of cardiovascular disease.[13] The ADA/ACC consensus report recommends, in addition to an LDL-C and non–HDL-C goal of 70 mg/dL and 100 mg/dL, respectively, an apo B goal of 80 mg/dL for patients with either established cardiovascular disease or diabetes with one risk

TABLE 3. **Effectiveness of Statin Therapy at Decreasing LDL-C, Non–HDL-C, and Apo B Levels in 11 Statin Trials[a,b]**

| | % Reduction on therapy | Mean on-treatment concentration (mg/dL) | Mean on-treatment population (%) |
|---|---|---|---|
| LDL-C | 42.1 | 99.2 | 21 |
| Non–HDL-C | 39.6 | 127.0 | 29 |
| Apo B | 33.1 | 101.6 | 55 |

[a] Apo B = apolipoprotein B; LDL-C = low-density lipoprotein cholesterol; non–HDL-C = non–high-density lipoprotein cholesterol.
[b] SI conversion factors: To convert apo B to g/L, multiply by 0.01; to convert LDL-C and non–HDL-C to mmol/L, multiply by 0.0259.
Adapted from *J Clin Lipidology*,[28] with permission.

TABLE 4. **ADA/ACC Consensus Report Treatment Goals in Patients with Lipoprotein Abnormalities**[a]

| Risk category | Goals (mg/dL[b]) | | |
|---|---|---|---|
| | LDL-C | non–HDL-C | apo B |
| Highest-risk patients, including those with (1) known CVD or (2) diabetes plus ≥1 additional major CVD risk factor | <70 | <100 | <80 |
| High-risk patients, including those with (1) no diabetes or known clinical CVD but ≥2 additional major CVD risk factors or (2) diabetes but no other major risk factor[c] | <100 | <130 | <90 |

[a] ACC = American College of Cardiology; ADA = American Diabetes Association; apo B = apolipoprotein B; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; non–HDL-C = non–high-density lipoprotein cholesterol.
[b] SI conversion factors: To convert apo B to g/L, multiply by 0.01; to convert LDL-C and non–HDL-C to mmol/L, multiply by 0.0259.
[c] Other major risk factors (beyond dyslipoproteinemia) include smoking, hypertension, and family history of premature coronary artery disease.
Adapted from *J Am Coll Cardiol*,[13] with permission from Elsevier.

factor.[13] In patients without cardiovascular disease but with 2 cardiometabolic risk factors, the ADA/ACC recommends an apo B goal of 90 mg/dL. For patients with coronary heart disease, the Canadian Cardiovascular Society recommends an apo B goal of 80 mg/dL.[2]

Data from recent clinical trials, including PROVE IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) and CARDS (Collaborative Atorvastatin Diabetes Study), lend support to an apo B goal of less than 80 mg/dL for high-risk patients. In PROVE IT, more than 4000 patients recently hospitalized for an acute coronary syndrome with a baseline median apo B level near 100 mg/dL were randomized to receive treatment either with pravastatin at 40 mg (moderate therapy) or with atorvastatin at 80 mg (intensive therapy).[29] At the end of the trial, the median apo B level for the moderate therapy arm was 90 mg/dL, whereas the median for the aggressive therapy arm was 67 mg/dL. The aggressive therapy arm experienced a 16% reduction in the HR for death or a major cardiovascular event (*P*=.005; 95% CI, 5%-26%) compared with the moderate therapy arm.

In CARDS, more than 2800 diabetic patients without documentation of previous cardiovascular disease were randomized to atorvastatin, 10 mg, or placebo.[30] Mean baseline LDL-C, non–HDL-C, and apo B values were 117 mg/dL, 152 mg/dL, and 117 mg/dL, respectively. Median duration of follow-up was 3.9 years. Compared with placebo, atorvastatin treatment at 1 year lowered LDL-C concentration by a mean of 40.9% (95% CI, 40.1%-41.6%), whereas atorvastatin treatment decreased the non–HDL-C concentration by 38.1% (95% CI, 37.2%-39%) and the apo B concentration by 24.3% (95% CI, 23.4%-25.2%) (all *P* <.001). There was a 37% risk reduction in the primary end point of major cardiovascular events (95% CI, 52%-17%; *P*=.001). The mean apo B level after 1 year of therapy with atorvastatin was 71.5 mg/dL.

Although these trials, which demonstrated significant cardiovascular event reductions, were not designed to test specific apo B targets, the levels of apo B that were achieved in these studies are consistent with the ADA/ACC apo B goals of less than 80 mg/dL for patients with known cardiovascular disease or with diabetes and one risk factor. There has been much discussion regarding the appropriate apo B goals of therapy. Some experts advocate using apo B goals equivalent to LDL-C in terms of population percentiles from databases such as the Framingham Offspring study (Table 5).[31] If this approach is applied to the updated NCEP III guidelines, high-risk patients requiring an LDL-C level of 100 mg/dL, which is the 20th percentile, should have an apo B goal of 78 mg/dL (Table 3). Likewise, patients at very high risk of coronary heart disease would require an LDL goal of 70 mg/dL, which is the second percentile, and the corresponding apo B level would be 54 mg/dL.

In our view, using the same population percentile cut-points for LDL-C and apo B is probably unnecessary. These apo B targets are not currently supported by any clinical trial evidence, and their use may result in unachievable goals with even 2 or 3 lipid-lowering drugs. Thus, the medical necessity and practical feasibility of decreasing apo B levels to less than 60 mg/dL (the second percentile) are questionable. In the EXPLORER (*Ex*amination of *P*otential *L*ipid Modifying Effects *o*f *R*osuvastatin in Combination With *E*zetimibe versus *R*osuvastatin) trial, patients were treated with the highest dose of the most potent statin, rosuvastatin at 40 mg, in conjunction with ezetimibe at 10 mg.[32] The mean baseline LDL-C and apo B values were 189 mg/dL and 176 mg/dL, respectively. Although this combination resulted in

TABLE 5. **Population Distributions of LDL-C, non–HDL-C, and Apo B in the Framingham Offspring Study**[a]

| % | LDL-C | non–HDL-C | apo B |
|---|---|---|---|
| 2 | 70 | 83 | 54 |
| 5 | 78 | 94 | 62 |
| 10 | 88 | 104 | 69 |
| 20 | 100 | 119 | 78 |
| 30 | 111 | 132 | 85 |
| 40 | 120 | 143 | 91 |
| 50 | 130 | 153 | 97 |
| 60 | 139 | 163 | 103 |
| 70 | 149 | 175 | 110 |
| 80 | 160 | 187 | 118 |
| 90 | 176 | 205 | 130 |
| 95 | 191 | 224 | 140 |

[a] Unit is mg/dL. Apo B = apolipoprotein B; LDL-C = low-density lipoprotein cholesterol; non–HDL-C = non–high-density lipoprotein cholesterol.
[b] SI conversion factors: To convert apo B to g/L, multiply by 0.01; to convert LDL-C and non–HDL-C to mmol/L, multiply by 0.0259.
Adapted from *Clin Chem*,[31] with permission.

a 70% reduction in LDL-C levels, the apo B reduction was significantly lower at 56%. At the end of the trial, LDL-C and apo B values were 57 mg/dL and 76 mg/dL, respectively. This trial highlights the difficulty in achieving apo B goals lower than 60 mg/dL. For patients in the EXPLORER trial to achieve an apo B goal of 54 mg/dL (the 2nd percentile), a third and possibly a fourth drug would have been needed.

## CONCLUSION

A substantial number of patients with atherosclerotic vascular disease have LDL-C levels in the recommended range but still have significant residual risk. This discrepancy exists because many of these patients have elevated LDL particle numbers despite having normal LDL-C concentrations. The calculation of non–HDL-C may improve risk prediction and assessment of goal attainment in many of these patients; however, the total body of evidence suggests that apo B is a better marker for total atherogenic particle number. The available evidence supports the superiority of apo B over LDL-C and non–HDL-C in both risk stratification and monitoring of the effectiveness of statin therapy. Although NCEP III is built on the strong foundations of LDL-C[1] and non–HDL-C,[4] consideration should be given to the use of additional markers that may further aid in better risk stratification and in greater reductions in residual risk.

### REFERENCES


**1.** Grundy SM, Cleeman JL, Mercz CN, et al; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines [published correction appears in *Circulation*. 2004;110(6):763]. *Circulation*. 2004; 110(2):227-239.

**2.** Genest J, McPherson R, Frohlich J, et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult-2009 recommendations. *Can J Cardiol*. 2009;25(10):567-579.

**3.** Mudd JO, Borlaug BA, Johnston PV, et al. Beyond low-density lipoprotein cholesterol: defining the role of low-density lipoprotein heterogeneity in coronary artery disease. *J Am Coll Cardiol*. 2007;50(18):1735-1741.

**4.** Blaha MJ, Blumenthal RS, Brinton EA, Jacobson TA; National Lipid Association Taskforce on Non-HDL Cholesterol. The importance of non-HDL cholesterol reporting in lipid management. *J Clin Lipidol*. 2008;2(4):267-273.

**5.** Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. *Am J Cardiol*. 1998;81(4A):7B-12B.

**6.** Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk*. 1996;3(2):213-219.

**7.** Sachdeva A, Cannon CP, Deedwania PC, et al. Lipid levels in patients hospitalized with coronary artery disease: an analysis of 136,905 hospitalizations in Get with the Guidelines. *Am Heart J*.2009;157(1):111-117.

**8.** Libby P. The forgotten majority: unfinished business in cardiovascular risk reduction. *J Am Coll Cardiol*. 2005;46(7):1225-1228.

**9.** Barter PJ, Ballantyne CM, Carmena R, et al. Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel. *J Intern Med*. 2006;259(3):247-258.

**10.** Chapman MJ, Laplaud PM, Luc G, et al. Further resolution of the low density lipoprotein spectrum in normal human plasma: physicochemical characteristics of discrete subspecies separated by density gradient ultracentrifugation. *J Lipid Res*. 1988;29(4):442-458.

**11.** Berneis KK, Krauss RM. Metabolic origins and clinical significance of LDL heterogeneity. *J Lipid Res*. 2002;43(9):1363-1379.

**12.** Otvos JD, Jeyarajah EJ, Cromwell WC. Measurement issues related to lipoprotein heterogeneity. *Am J Cardiol*. 2002;90(8A):22i-29i.

**13.** Brunzell JD, Davidson M, Furberg CD, et al. Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. *J Am Coll Cardiol*. 2008;51(15):1512-1524.

**14.** Cui Y, Blumenthal RS, Flaws JA, et al. Non-high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. *Arch Intern Med*. 2001;161(11):1413-1419.

**15.** Frost PH, Havel RJ. Rationale for use of non-high-density lipoprotein cholesterol rather than low-density lipoprotein cholesterol as a tool for lipoprotein cholesterol screening and assessment of risk and therapy. *Am J Cardiol*. 1998;81(4A):26B-31B.

**16.** Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet*. 2001;358(9298):2026-2033.

**17.** McQueen MJ, Hawken S, Wang X, et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. *Lancet*. 2008;372(9634):224-233.

**18.** Hsia SH, Pan D, Berookim P, Lee ML. A population-based, cross-sectional comparison of lipid-related indexes for symptoms of atherosclerotic disease. *Am J Cardiol*. 2006;98(8):1047-1052.

**19.** Holme I, Cater NB, Faergeman O, et al. Lipoprotein predictors of cardiovascular events in statin-treated patients with coronary heart disease: insights from the incremental decrease in end-points through aggressive lipid-lowering trial (IDEAL). *Ann Med*. 2008;40(6):456-464.

**20.** Simes RJ, Marschner IC, Hunt D, et al. Relationship between lipid levels and clinical outcomes in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Trial: to what extent is the reduction in coronary events with pravastatin explained by on-study lipid levels? *Circulation*. 2002;105(10):1162-1169.

**21.** Chien KL, Hsu HC, Su TC, Chen MF, Lee YT, Hu FB. Apolipoprotein B and non-high density lipoprotein cholesterol and the risk of coronary heart disease in Chinese. *J Lipid Res*. 2007;48(11):2499-2505.

**22.** Gotto AM Jr, Whitney E, Stein EA, et al. Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Circulation*. 2000;101(5):477-484.

**23.** Bruno G, Merletti F, Biggeri A, et al. Effect of age on the association of non-high-density-lipoprotein cholesterol and apolipoprotein B with cardiovascular mortality in a Mediterranean population with type 2 diabetes: the Casale Monferrato study. *Diabetologia*. 2006;49(5):937-944.

**24.** van Lennep JE, Westerveld HT, van Lennep HW, Zwinderman AH, Erkelens DW, van der Wall EE. Apolipoprotein concentrations during treatment and recurrent coronary artery disease events. *Arterioscler Thromb Vasc Biol*. 2000;20(11):2408-2413.

**25.** Pischon T, Girman CJ, Sacks FM, Rifai N, Stampfer MJ, Rimm EB. Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. *Circulation*. 2005;112(22):3375-3383.

**26.** Kastelein JJP, van der Steeg WA, Holme I, et al. Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. *Circulation*. 2008;117(23):3002-3009.

**27.** Ballantyne CM, Bertolami M, Hernandez Garcia HR, et al. Achieving LDL cholesterol, non-HDL cholesterol, and apolipoprotein B target levels in high-risk patients: Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapY (MERCURY) II. *Am Heart J*. 2006;151(5):975.e1-975.e9.

**28.** Sniderman AD. Differential response of cholesterol and particle measures of atherogenic lipoproteins to LDL-lowering therapy: implications for clinical practice. *J Clin Lipidol*. 2008;2(1):36-42.

**29.** Ray KK, Cannon CP, Cairns R, Morrow DA, Ridker PM, Braunwald E. Prognostic utility of apoB/AI, total cholesterol/HDL, non-HDL cholesterol, or hs-CRP as predictors of clinical risk in patients receiving statin therapy after acute coronary syndromes: results from PROVE IT-TIMI 22. *Arterioscler Thromb Vasc Biol*. 2009;29(3):424-430.

**30.** Charlton-Menys V, Betteridge DJ, Colhoun H, et al. Targets of statin therapy: LDL cholesterol, non-HDL cholesterol, and apolipoprotein B in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS). *Clin Chem*. 2009;55(3):473-480.

**31.** Contois JH, McConnell JP, Sethi AA, et al. Apolipoprotein B and cardiovascular disease risk: position statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices. *Clin Chem*. 2009;55(3):407-419.

**32.** Ballantyne CM, Weiss R, Moccetti T, et al. Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORER study). *Am J Cardiol*. 2007;99(5):673-680.